DR. STANTON: I'll make a quick comment and then I'll turn it over. A lot of the data on atrial stunning is in longer lasting atrial fibrillation when people then came in for subsequent external cardioversion. I don't know that we have data specifically addressing stunning in the acute setting with this device.

Also, there's obviously additional benefits that people get in terms of symptomatic relief probably more do to the rate control than actually necessarily the restoration of the atrial contribution, although people with heart failure, I think the atrial contribution does play a significant role.

DR. SCHWARTZMAN: Yes. It's kind of interesting. It's very hard to answer that question. I think as has been stated earlier, the restitution or the symptom relief is a combination of control of rate, control of irregularity or eradication of irregularity and the issue of what is the independent value of atrial contraction, A-V synchrony.

We have no data regarding first of all the

duration of atrial fibrillation related -- and its related mechanical implications in device patients and we have no data in terms of subsets of patients, in other words, comorbid heart disease, for example. What is the relative importance of each component? What I can tell you is clinically it's interesting to watch the patients with more advance structural heart disease have a longer lag to symptom reduction. In other words, a patient with heart failure can take a couple of days to realize their full symptom benefit from or stored sinus rhythm with a relatively well preserved heart goes back quickly. I don't know what that means, but these are some of the issues related to your question.

DR. CRITTENDEN: And the symptom benefit is more -- better exercised tolerance or is it lack of palpitations?

DR. STANTON: I'll tell you what, let me ask Dr. David Newman to come up. He did in-depth analysis of the quality of life issues.

DR. NEWMAN: My name is Dr. David Newman from the University of Toronto. And I have no

financial relationship to the company and have received ample reimbursement of honorarium.

The question on symptoms that you ask is obviously a key one. There's a -- you should understand that the respond stem to the questions asks the patients to integrate one month worth of data. So it's not as though there's an impact of shock analysis scale that is at least well validated that's available to us in analysis which would be most germane to your question. It's reasonable to surmise that in some patients there's a benefit due to rapid restoration of rate. The symptom check list that was used was the validated instrument of Blouvian, et al. from Alabama and in that one I can at least tell you that as you already saw there is a very significant decrease in arrhythmia related symptoms from baseline to 3 months persisting at 6 months with a significant change in the score. This symptom checklist as you may know has eight symptoms in particular that are highly related to arrhythmia, sensations of rapid heart action, heart skipping, light headedness, things of that nature. The larger symptom hit was on as perhaps you would

expect, those symptoms of heart racing, heart fluttering, heart skipping, things of that nature and that was seen above baseline and at six months with less than a symptom hit, so to speak on score changes which were still significant, but not as great on those particular items related to chest pain, dyspnea and so forth. If that answers you.

DR. CRITTENDEN: Just one final question for you, in particular, is there any drift in the SF-36 scores in the normal population? I know when my partners go on vacation, I've got to work harder. My SF-36 scores go down, I'm sure.

(Laughter.)

So I mean you use is a base of comparison, but I was wondering how stable it is from baseline in a population of quote unquote normals. That may be kind of unrealistic.

DR. NEWMAN: Sure. There is some data showing -- we have measured the SF-36 in a different cohort of patients of 150 patients who all had tertiary care referral, refractory atrial fibrillation, drug refractory atrial fibrillation.

And they like this population that's in your package, have very similar impaired quality of life at baseline. And in that particular group of patients measured over 3, 6 and 12 months, their impaired quality of life was consistent over that entire time period.

Clearly, in this data set, that is reasonable inferential data supporting efficacy, since in this data set there was a very dramatic improvement in health-related patient perceived quality of life over the baseline 3 and 6 month time period. And it's difficult to believe that that would spontaneously get that much better over time. The magnitude of improvement, thinking of the first speaker was really quite dramatic. We're talking -- in the quality of life literature measuring differences as we all know a challenge. The standard that people use is something called the effect size. It's taking into account the inherent variability in this measure relative to its absolute change. It's quantified in standard deviation units.

So for example, in 4 to 5 scales in this

data set, we're having effect size in the order of half a standard deviation. This is quite remarkable. You can say it's quite remarkable because this SF-36 data base has a large number of normative disease populations within it. So it's comparable, for example to the kind of difference you have between uncomplicated hypertension and patients who have had myocardial infarction, just to give you a metric that's clinically relevant. That's quite dramatic.

The only other comparator I can offer in the atrial fibrillation world is data for the efficacy of amiodarone therapy, arguably, one of the better drugs that we have available for atrial fibrillation where in the Canadian of atrial fibrillation, for example, that data group has associated with their efficacy a quality of life improvement in the order of around a third of the standard deviation, just to give you some sense they're different groups.

And lastly, as one would expect, there's a degree of convergence. We have found when we analyze the change in symptoms score that there is indeed a correlation with the change in quality of

life score, at least supporting the validity of these tools we're using that a correlation and symptoms attributable to rhythm was associated with a similar change in the direction of improvement in quality of life on the generic instrument.

DR. CRITTENDEN: That's all.

DR. TRACY: I think there is no other entity other than atrial fibrillation that poses a challenge to the clinical management. It is a very difficult thing to deal with clinically and patients are very symptomatic. We have to have a number of tools available to help people who have this condition. This tool, however, I agree with Tony. There are some questions about the safety and efficacy of this device that I would just like to discuss with you.

You had 113 centers working for two years to come up with 146 patients. Now unless these folks were seeing two patients a year, I think that you must be looking at less than 5 percent of the total atrial fibrillation population. You're talking about a very tiny niche here for this device to treat a disease

which does impose some negative prognostic significance. I do think that there is increased mortality in a-fib if you correct for other factors. But still, it's a pretty tiny group of people we're talking about. Is that -- am I right in this assessment?

DR. STANTON: Yes. I think that's an important point, that this is a very specific portion, small portion of the large group of atrial fibrillation patients and you've identified it very well.

DR. TRACY: You know, the other treatment that we have for a-fib that might be considered kind of wild and crazy, but it's very effective is the maze procedure which carries -- this device had a serious complication rate of somewhere around 15 percent and a failure rate with either explant or A-V node ablation in 13 percent.

Compared to the maze procedure, this is really bad. The maze procedure has a much higher success rate with lower attendant risks and this is -- we're talking about surgery here. This is kind of

hard to stack. I know these are not direct comparisons and I'm using data from surgical literature versus very controlled information here, but I think you have to put that into perspective somehow.

DR. SCHWARTZMAN: You know, the perspective I have is with respect to what "serious" means. There's no mortality in this study, (a). (B), there's the potential ancillary benefit of ventricular tachyrhythmia backup, neither of which is -- which is not addressed by the maze procedure.

You know, the issue of lead dislodgement is real. The issue of A-V node ablation, even though is described in the company literature as a failure of strategy, in my experience has not necessary met that. For example, I've had patients who could not tolerate rate-controlling drugs in whom we did the A-V node ablation to allow the device strategy to go forward.

My own feeling is that if I took 10 patients, it depends on the literature you read, but let's say there's a 1 to 2 percent rate of mortality from a maze procedure. Notwithstanding the morbidity

which I think is considerable at the long cross clamp times, etcetera, that those serious complications are worse than the serious complications we are talking about with this device. So I don't think serious is a generic term. I think you really have to talk in specifics. My feeling is that this strategy is effective and that I'm not putting patients in the way of mortality related to the deployment of the strategy.

DR. STANTON: Yes. I think that it's important that -- we keep coming back to the complications. It's important that we really look at what the complications are and particularly when you're comparing with something like the surgical maze and the morbidity associated with that. There were 11 lead dislodgements. Those are all correctable. Albeit with a second procedure, but compared to a sternotomy which is done in the maze procedure, i would argue that it's -- or a thoracotomy -- that it's a less morbid -- it's still a less morbid procedure to go back in and reposition a lead.

DR. GOLD: And again, the maze procedure,

to my knowledge, was never placed under the scrutiny of this sort of regulatory approach to documenting what we classify as a very low threshold as a complication.

Again, Cindy, you've probably had the best experience being in a center with very confident maze procedure surgeons there, but pacemaker implantation rates for maze procedure have been quoted as quite high, except in one or two hands where there are reported lower rates. No one is talking about the sternal wound infections, the recuperation time, the hospitalization time, so on and so forth. So I really think that this is the complication rate of this device, if I had the choice of having the two, I think it's quite clear which one I would have, but we just don't have the data on the maze procedure of knowing what the complication rate for that procedure is, using the criteria that the FDA requires for doing an IDE study.

DR. STANTON: And Cindy, I don't want to minimize the complications by any means. The complications are what they are. They are consistent

with complications of device-based therapy. We're up front about that. We think that as with any therapy that's delivered to patients, patients need to know what the benefits are and what the risks are.

DR. TRACY: Yes. Your points are well taken, that the maze was never subjected to this type of scrutiny where there had to be every type of complication listed, but still as the patient is sitting in your office and you're gaining consent for this, they're at no risk for any of these types of things. So they're not going to drop dead in front of you unless there's some ventricular arrhythmia that you don't know about. They're not going to have some other thing happen to them. It's a relatively low risk disease, at least at any given instant that we're putting in a device that carries some attendant risk and I think we have to define carefully the group of people that we want to and looks like just from the obvious difficulty recruiting patients into this study, I don't think it's going to be much of an issue to reassure Tony. I don't think that people are going to be jumping out saying please put this device in me,

because I think it's a relatively small group of people who are as intelligent and motivated as these two were today to come -- who will have this device implanted and I think that's probably the best thing -- the best safeguard that we have on this device.

A couple of discouraging findings that sort of came out here are -- it's discouraging how poorly the antitachy pacing was. It's discouraging how the pacing algorithms to prevent atrial fibrillation, how poorly they worked. Is that --is there any point in even programming these things on?

Was there any other benefit that people got from their rates moving algorithms? Clearly, it didn't prevent atrial fibrillation, but did it make them feel better by reducing their symptoms of palpitations? Do you have any data on that that would support the use of these modalities?

DR. STANTON: So you're not talking about the termination, you're just talking about the prevention?

DR. TRACY: I'm talking about prevention. Also, we'll talk about termination. Because it didn't

look like a great deal either, but let's just talk about prevention.

DR. STANTON: In the prevention study that we did, we were not able to show that prevention prevented atrial fibrillation. However, there was no adverse effects to that. Specifically on your question, we did not look at whether there was a reduction in symptoms that we could attribute to the prevention algorithms. Certainly, a number of these prevention algorithms would have the potential, although unproven, of reducing some symptoms. We would not claim that in the labeling.

DR. TRACY: So that wasn't captured in the quality of life data?

DR. STANTON: No, it couldn't be captured.

DR. TRACY: I think it's kind of hard to figure out how you could ever burst somebody out of a-fib. I've tried. We've all tried in the EP lab to burst people out of a-fib. I'm surprised you even tried and put that in as a pacing potential therapy for a-fib and it didn't work, so why is it there? Why should we use it? Is it a programmable OFF, is it

something we should put a warning, P.S., this doesn't work?

(Laughter.)

DR. STANTON: For all the atrial episodes, atrial pacing therapies, ATP and high frequency burst worked about a third of the time. And if you keep in mind that's a freebie. That's a patient who didn't have to go on to have a shock to terminate their arrhythmia. So I think there's that additional benefit that you get. As we've talked before with an overall success rate of 91 percent, that is with a shock-based therapy. That's the main intent. This is additional potential benefit that patients can receive.

DR. GOLD: I would point out that again there is virtually no risk or no risk that was measurable of giving pacing therapy, no complaints from patients of these short episodes of pacing therapy and if a third of these episodes we can early termination, we don't have to wait hours or whatever, we intervene early and a third of these episodes overall can be terminated with pacing therapy, why

not?

DR. SIMMONS: Can I jump in here? Do you mind?

DR. TRACY: Go ahead.

DR. SIMMONS: Where did you get this one third number? My reading, looking at the data is you're effectiveness to this 50 hertz burst for atrial fibrillation was around 17 percent and your effectiveness for a regular tachycardia for this 50 hertz burst was 15 percent. I'd like to see some of those conversions too.

Was this just the fact that by programming in 50 hertz, ATP 50 hertz, ATP 50 hertz, ATTP, you finally, the patient spontaneously converted because they all are spontaneously converting anyway? I mean that was one of the things that I didn't get around to -- so your effectiveness data for the 50 hertz burst isn't 30 percent, it's 10 to 15 percent.

MR. BROWN: Yes, I believe the numbers that Marshall was saying were overall numbers for pacing efficacy for all atrial episodes. That number, the raw number is 34.9 percent.

You're quite right in that the high frequency burst numbers of the raw efficacious are 18.2 percent and 11.7 percent respectively.

Now in regards to the idea that -- if you simply give enough therapies, eventually the thing terminates spontaneously, we did have cases where episodes were treated with a sequence of therapies and in some cases it did go ATP high frequency burst and back and forth.

What we find when we subanalyze those numbers and that table is available in the clinical summary on page 15, that's a table of all therapy sequences delivered. What we find is that the vast majority of pacing terminations, if you're going to have a successful termination it occurred either on the first or perhaps the second pacing therapy delivered. So you may have gone ATP 50 hertz burst, gotten a termination then, but basically if you went back and forth and back and forth which did happen occasionally, it did happen rarely and very, even more rarely were those terminations successful.

DR. SIMMONS: That's on page 15?

MR. BROWN: Yes, of the clinical summary.

DR. SIMMONS: It gives you the sequences and it gives me what percent were successful. It doesn't tell me which therapy worked.

DR. TRACY: I guess the bottom line is it's not a great therapy. Is that fair to say?

DR. STANTON: I think it's not the main therapy of the device. I think it's an additional therapy that helps a number of patients to avoid having to either deliver themselves shock or have an automatic shock.

DR. TRACY: Does it ever delay more appropriate therapy? I mean the fact that it's not a great therapy, it doesn't seem to work. It's certainly not going to work in those that are specifically a-fib. The percent success in a-fib has got to be very, very low. Is it ever going to delay appropriate therapy?

DR. STANTON: The therapies are programmable as to how much delay after the onset of detection of the atrial fibrillation so that clinician has the capability to independently delay the pacing

therapies and the shock therapies and David, if you want to maybe make any comments about how you might choose that?

DR. SCHWARTZMAN: The patient can override. If it's in the window of the hard window that you program for availability of shock, even if patient therapies are on-going. Let me just say I look at this data differently. I have the same preconceived bias that this will never work because I entered into the picture with this multi-wave re-entry mechanism in my head, but -- and there are problems. For example, there's clearly a component of true, true and unrelated, that is pacing is going on, the atrial arrhythmia stops, but they're not related. But I can tell you that a majority, the therapy is delivered and the arrhythmia stops. Now whether that was coincidental or not, we can argue about it, but I would say no.

Two ways this happens. One is the -- and the problem is reading from a local bipole just what the global atrial rhythm is. So, for example, if you're in the right atrial appendage, your electrogram

may look very regular with multi-wave re-entry because it's an anatomically constrained area. So the science is a little difficult to draw from the clinical experience, but if you look at the way these things terminate, either they terminate because you have presumably a uniform rhythm, you pace into it and you're dealing with a relatively macro-entry circuit, or you're dealing with a macro-entry circuit that degenerated into a multi-wave circuit that cannot sustain itself because of the pacing. So one way or the other this is -- in a substantial population, I believe it as substantial. There is pacing attributable termination which -- and the lesson I draw from this is that atrial fibrillation is not always atrial fibrillation. There are periods where it becomes its no so sinister cousin, the macro-entry circuit that may be amenable to pace termination which to me, this data is extremely promising in terms of making devices, in terms of pacing site or availability of pacing with the device given more information as to when things are relatively uniform versus when they're not, etcetera, etcetera. I find

this to be very promising data, but I agree with you in its current iteration I would say it has limited efficacy. It's surprising to me nevertheless.

DR. GOLD: I would just point out it was not part of this study, but with the same device in the VT/AT population who had both arrhythmias. There was a randomized study of turning pacing therapies ON versus OFF with prevention therapies. And that study showed a very marked reduction in arrhythmia burden using these therapies. So I think although the raw number as we think of ventricular tachycardia, we want to pace terminate 90 percent of them and SVTs, when we used to put in anti-tachycardia devices before ablation we could pace terminate them. For these, often disorganized irregular rhythms, by being able to intervene early because usually shock therapy is not given immediately. Patients wait to give shocks or their program is nocturnal shocks. By being able to intervene early the minority of patients of episodes that we can pace terminate significantly reduces the arrhythmia burden and duration of episodes for patients with no measurable price to pay for that.

DR. STANTON: And what Michael is referring to in that study was an 89 percent reduction in arrhythmia burden and that was statistically significant. That was in the VT/AT study.

Let me also just make one other point and that is that in the sequence of pacing therapies, high frequency burst follows ATP, so in most of these cases ATP had already failed until it was again an additional opportunity for the patient to pace terminate.

DR. TRACY: Does that make sense to you, Tony?

DR. SIMMONS: I'm not sure what he's saying. What he said did. I'm not sure what Marshall -- showing 50 hertz being the primary therapy in a lot of these, more than half.

DR. STANTON: In the AT zone you have ATP and high frequency available. In the AF zone, only high frequency, so there it's going to be high frequency by itself.

In the AT zone most of the time it's going to follow ATP.

DR. SIMMONS: There are certainly a lot of 50 hertz bursts here as the primary therapy on this chart. But anyway, that's okay. I like to -- you know, back when we were doing the Orthocor and the Pasars and all those anti-tachy pacing algorithms for SVTs before ablation, a lot of the time what we did was accelerate the rhythm into a-fib and then the a-fib was nonsustained. And I just wonder if that's not what's happening here more than the therapy is working.

DR. GOLD: Even if it is, it's successful.

DR. SIMMONS: Ten percent of the time, 15 percent? If it doesn't cost anything, it's probably worth trying.

DR. STANTON: If redetection had occurred, if it had accelerated it to a-fib and redetection had occurred, then that would have been counted as a failed episode, is that correct?

No. Strike that from the record.

(Laughter.)

DR. TRACY: This is a complicated device. Okay, I think if you somehow could have convinced

these two folks to come into the hospital every time that they had shocks or every time that they had an episode of a-fib, even though it was intrusive in their life, and shocked them, that the percent in sinus rhythm would be the same as it is with this device. So you know, the percent in sinus rhythm at two years was what again?

DR. GOLD: Eighty --

DR. TRACY: Eighty percent. Okay, so a little bit higher than very --

DR. SCHWARTZMAN: That's not true. No, that was the number who still had the device.

What the study decided to do and I don't agree with this, is that they took everything. They called A-V node ablation therapy failures, they called explants therapy failures, but A-V node ablations did not answer your question because in my own experience half of my A-V node ablations were to facilitate device therapy and all of those patients were in sinus rhythm.

DR. TRACY: Okay.

DR. SCHWARTZMAN: So that number is a low

ball figure. I think we're talking more like 90 percent at two years.

DR. TRACY: Ninety percent, two years in sinus rhythm.

DR. GOLD: Ninety-four percent at one year were in sinus rhythm as part of the study.

DR. TRACY: Okay.

DR. SIMMONS: That's been throughout all the explants.

DR. GOLD: No, the explants are considered therapy failures.

DR. STANTON: That 90 percent does take into the account the people, in the 10 percent that were not in sinus includes the device explants.

DR. TRACY: Okay, so 90 percent, somewhere between 80 and 90 percent.

DR. STANTON: Ninety percent at one year. At the one year follow-up visit, 90 percent of people were in sinus rhythm and had their device. The therapy survival curve, if you will, that we showed there went out to two years and was at 80 percent of people, 80.9 percent still had their device in and it

was still functioning.

DR. TRACY: And of those 80 percent who still have the device, what percent were still in sinus rhythm?

MR. BROWN: There are actually two separate analyses being discussed here. The analysis that we're mostly discussing is the analysis of what you might call device survival therapy survival which is taking into account all patients with explants, all patients with A-V nodal ablations, all patients with device therapies turned off and also, in fact, the two failures to implant at the start of the study. Those numbers have an 89 percent survival rate at one year and 81 percent at two years.

The question of patients in sinus rhythm was actually analyzed separately by interrogating the device at the various follow-ups and asking was the patient in sinus rhythm at the times of the 1, 3, 6 and 12-month follow-ups. Those numbers are ranging from 90 to 95 percent. Ninety percent of patients were in sinus rhythm at the time of their one month follow-up, running up to 94 percent at the time of

their 12-month follow-up. So these are distinct concepts that we're discussing.

DR. TRACY: Ninety-four percent of those who still had a device that was functional?

MR. BROWN: That's right, at the time of the follow-up itself.

DR. TRACY: At the time of the follow-up which would be approximately 80 percent of the patients?

MR. BROWN: Well, it would be a total of --

DR. TRACY: At two years.

MR. BROWN: About 85 percent.

DR. TRACY: Eighty-five percent, okay. Somewhere in that vicinity, I still don't know the answer to the question of those who had the active device how many were in sinus rhythm. I guess I'm still confused on that point.

MR. BROWN: That's that one year number, 94 percent.

DR. TRACY: Ninety-four percent, okay.

MR. BROWN: That's right.

DR. TRACY: Which is better than other available therapies at maintaining sinus rhythm, but probably not better than if had somehow managed to convince these people to come in every time they went into atrial fib. So your biggest selling point probably here to convince me is that it's more in the quality of life issues rather than the efficacy of this therapy.

DR. STANTON: The only comment I'd make there and this is just hypothesis is we don't know whether what you said is true. It may be, but a lot of asymptomatic episodes would have been treated with nonshock therapies and so what role that would have played, don't know.

DR. TRACY: Well, that's another question I had. If you had a patient who has a patient activator and then you subsequently interrogate them, what percentage of those patients, as we all know, many of these people will have asymptomatic episodes they're not aware of.

What percent of those people did not receive therapies for episodes of atrial fibrillation

and is there some caveat there that you've already mentioned like that people must remain on anticoagulation. I think if it's solely based on patient activated, and it happened to be the three months where the automatic things were turned off, you could miss episodes.

DR. STANTON: No question. That would be analogous to anti-arrhythmic drug therapy or any other therapy. Here, we have the opportunity for clinicians though of actually documenting how much atrial fibrillation the person is having. So should the clinician choose to adjust anticoagulant therapy, they would have more information on which to make that decision.

DR. TRACY: And do you have any information on what that number was, what percentage of asymptomatic episodes there were? Because one could argue that if a person is having asymptomatic atrial fibrillation that's okay anyway, as long as they're anticoagulated and they should not be treated. So it would be kind of scary if you were sitting in your car and you didn't have the patient activator, it

was set on an automatic mode and you were asymptomatic and the thing shocked you. What's the protection against that happening?

DR. GOLD: The device is programmable when to shock patients. So when we have automatic shocks on and we're not using a patient activator, we always make them nocturnal shocks, so if a patient tells us that they go bed at 11 and wake up at 7 in the morning, if we're going to give them a shock, we normally give it to them at 5, 6 o'clock in the morning so that the chance of them doing anything at the time is very low there. Adverse reaction to the shock is lower because they're asleep and we haven't ruined their night of sleep anyway because they've completed most of it before they got a shock. But we don't normally active, we've never activated these shocks. They just sort of go off as soon as they go into atrial fibrillation.

DR. TRACY: It would be a heck of an alarm clock.

(Laughter.)

DR. GOLD: Some of us need that kind.

DR. TRACY: Some days. So the answer to the question of the number of asymptomatic episodes, do you have that information?

MR. BROWN: Unfortunately we don't have information on that.

DR. TRACY: Okay. Then the only other thing that I could think of that would need some kind of like gigantic bold red flashing signs is that the fact and both Tony and I read through this and didn't pick that up that during ATP and high frequency bursts there is no ventricular backup and that has to be put like a flashing "Danger, Danger, Will Robbins." This is a very potentially dangerous thing if somebody doesn't realize that.

What do you have there that like flashes with red lights?

DR. STANTON: It would be highlighted in the warnings in A-V node ablation, post-A-V node ablation.

DR. TRACY: That's not good enough. It has got to be in the programmer, some warning that comes up and says if you -- during anti-tachy pacing

and high frequently bursts, there is no V backup. That just is mandatory.

DR. CONLEY: But I think that's only an issue in patients that have had an A-V nodal ablation. That's why we have that warning in there.

DR. TRACY: I don't think I'm comfortable with that. I think that that's still one of the potential -- I mean you can't program a unipolar to bipolar pacing without some kind of giant flashing lights coming on and telling you hey, don't do that. You can't do that. But you're allowing a potentially legal programming modality to be put in here without something coming up on the programmer. I think that's a serious problem with this. I didn't realize that until it came out here.

DR. STANTON: Could you explain a little bit about potentially lethal?

DR. TRACY: Suppose a physician does not read the warning, does not know that there is no backup during the anti-tachy pacing. And they do an A-V node ablation either to permit the device to continue functioning or for whatever reason that they

do not de-activate the anti-tachy or high frequency burst pacing, then you're leaving a situation where a patient could be asystolic for however long it takes for the device to go through its sequence of pacing.

DR. STANTON: No, it's not through the whole -- it would be through each delivery.

DR. TRACY: And how long is a delivery?

DR. STANTON: Maximum for a high frequency burst would be 3 seconds.

DR. TRACY: And how about for the anti-tachy?

DR. STANTON: For anti-tachy, in most cases it's going to be less than that. Do we have the data? Ten pulses. So it's less than -- it's 2 to 3 seconds max there also, so under 3 seconds.

DR. TRACY: Okay.

DR. STANTON: I acknowledge with you that there is a chance of pre-syncope in rare instances, perhaps syncope.

DR. TRACY: Or stroke-related to hypoprofusion and somebody with cerebral vascular disease, all sorts of things can happen. I mean a

2-second pause in a healthy person is nothing. But a 2 to 3 second pause in somebody with critical carotid disease is something.

I still think it's a serious issue that has to somehow be recognized here.

Just a couple of very quick questions. The short coil lead versus the standard lead. Is there any other functional difference in that lead, any difference in materials, any other concerns regarding that lead?

MS. MOYNAHAN: Could you use the microphone and introduce yourself, please?

DR. STANTON: It's an outer insulation of polyurethane on top of the inner silicon.

MR. HOLLEMAN: Tim Holleman from Medtronic. It has an outer polyurethane insulation. It's there primarily for stiffness.

DR. TRACY: Okay, and the -- any differences in the patient assistant versus the patient activator other than size in terms of --

DR. STANTON: There are some features that make it a little bit more user-friendly. It can

provide light and tone as opposed to just tone. It also provides the ability for the patient to question the device as to whether it's in atrial fibrillation without compelling it to deliver a shock.

DR. TRACY: Okay, and I guess, just in case nobody else asks the question -- one of the questions the FDA had asked was why was the event rate higher in this group than in the presumably sicker single chamber defib. group?

DR. STANTON: Statistically, there is no difference in the event rate and just by -- if you want to look at comparators of numbers without looking at statistics, it's really, in essence, the same as it was in the 7250 VT/AT trial.

DR. TRACY: Okay, Dr. Hartz?

DR. HARTZ: I'll identify myself since I came in a few minutes late, Renee Hartz, cardiac surgeon at Tulane.

My comments fall into everything except the device. I think the electrophysiologists have done a good job with that and if it was just the device, we'd probably be out of here by noon.

However, I have a lot of other serious issues.

Firstly, the patient activator, I'm very grateful for these patients who come to tell us how this actually works. However, this new activator, if you read this page, I cannot understand these warnings. I don't understand why there are four lights on a device and I can tell you that this room does not represent clinical reality. We have two very intelligent patients here and they probably could read this better than I can, but the patient population I have dealt with could not work this device. So several questions. Are the patients tested for hearing loss of any of the various frequencies? Because if I had this device on my left side, I could not hear a warning. If I had it on my right, I could. Hearing losses are more common than visual losses in this age group of patients.

What this leads to is is this device, because it's very complicated in design quotes for highly motivated, highly symptomatic patients, going to eventually be withheld from the less educated, less intelligent patient? That's a very serious problem.

DR. STANTON: Let me make a quick comments about the design and then turn it over to the clinicians.

The 9465 which is the newer version that we're asking for approval on has lights in addition to the tones.

DR. HARTZ: Yes, that's what I'm looking at, 9465. And there's too many lights. Probably a red and a green would be great, somehow or a red or green, yellow max. But then to put this blue light -- detection -- my patients could not understand this. So I would be very concerned that the patients are tested for hearing and there's a much more simplistic mechanism of operation.

So I'm concerned about the activator, virtually more than anything else.

The second thing is -- do you want to make some comments on those?

DR. SCHWARTZMAN: I certainly can't exclude your concerns. I share them.

I can tell you we have used the same technique in consecutive patients. I'll describe it,

what it is. I can tell you that these patients come from a range of educational backgrounds, socio-economic backgrounds and nevertheless it's biased just based on who they are. So I really can't get at the guts of your concern which is what happens when you just display this broadly.

But what we do is on the day after implantation, the morning which is generally the discharge morning, we do atrial fibrillation through the device and after a teaching session which is performed by my nurse. It takes a person through the device and I think you have a copy of the card, of a typical card that we give the patients which is a handwritten card, that is, handwritten in the presence of the patient. So obviously this takes some talent and experience on the part of the nurse, but a lot of this is education, a lot of medical care is education, so assuming that's effective, we induce the atrial fibrillation and we have the patient and their spouse in the room when they go through the sequence. And so that's the first step. And so obviously, the intactness of perception with respect to the tones is

there.

On this particular activator we rely more on the tones than the lights and patients usually respond fine to that. For at least the first shock and generally the first several, the patients page me when they're considering shocking themselves and I've actually on the phone when they do it. So just create another level of security in terms of their transition between implant and veteran status and then with very few exceptions after X number of events, they're on their own.

So the transition has not been very difficult and there are no patients in my experience that have been unable to learn how to use this. As you say, there are variable rates at which they do, but it starts, in my opinion, with going through a scenario that would play out at home with everybody in the room including physician and the nurse, spouse, etcetera. That has worked well.

Whether I can address your concern of the general population, I doubt it, but that's what I can tell you in terms of our experience.

DR. HARTZ: We have a lot of patients who can't read. And if you work in a lot of States and public institutions, I'm just saying that I think for the sake of information gathering and testing this device, you're dealing with the correct population. But in the long run, I'm afraid that something so accurate may lead to withholding of a device in a population that needs it more. My concern is about the activator.

The second thing is, concerns the lead and I share Dr. Simmons' concerns, why is this lead in this protocol? What is the definition -- when does a lead dislodgement become a complication? We surgeons when we put in leads try purposely to get them to dislodge before the patient leaves the hospital. All the old bans about moving arms and whatever -- because you want the lead to dislodge while the patient is under treatment and go back and I don't consider that much of a complication if you have to reposition a lead.

So in cardiology and electrophysiology why is it, when is this defined as a complication?

DR. STANTON: It's defined as a complication if a surgical intervention has to be done to correct it.

DR. GOLD: If you have to intervene on a lead, it's a complication. So every lead dislodgement by your criteria is a complication.

DR. HARTZ: Okay, I don't think that's a very serious complication. As a matter of fact, I would encourage repositioning leads. So I don't share your concern that that's a big deal, that number, but I really would encourage that the lead really does not have a whole lot to do with this. The lead in question does not have a lot to do with this protocol.

The other thing I want to clarify, the maze procedure has been mentioned several times and for all intents and purposes, that's not the only surgical option. The Maze III, the Cox Maze for all intents and purposes is almost a dead procedure and is a morbid big deal. But Dr. Aziz asked do you know if this is coming from the right or left side. A right sided maze is a very low -- carries extremely low morbidity and mortality. So if you knew you had a

right sided atrial fibrillation and could do a right sided maze and I'll get into something a little further, that would carry almost no risk to the patient, especially if the surgeon, while they were in the chest slipped a ligature over the left atrial appendage. Again, you wouldn't have to cross the aorta or anything to do that procedure.

You have to clarify the therapies -- the Japanese are designing all new forms of variance of the maze also. What we did not talk about was ablation. I would imagine all the investigators in this protocol have access to ablation devices. And in this very small group of patients which ones do you decide get the defibrillator rather than an ablation? Ablation would be fare more definitive.

DR. GOLD: Ablation, as it's currently approved and as we standardly use it, is for patients with organized monomorphic type of tachycardia such as superventricular tachycardia, atrial flutter. I think we all agree that this is a very inappropriate device for those sorts of arrhythmias that we can cure with standard catheter ablation. There certainly has been

a lot of enthusiasm and investigation of trying to use ablation technology for the treatment of atrial fibrillation. There's probably a small subgroup of patients with focal atrial fibrillation and we could debate how large that subset is, but at least in my hands a group of patients who have a focal source tend to be those with no structural heart disease, young patients with paroxysmal atrial fibrillation in whom there's some encouraging data that there may be a pulmonary vein source of those and some of those can be cured although the complication rates from that procedure have been troubling. That's not an approved indication for an ablation, but it is being done.

In terms of catheter type of maze procedures for the more typical atrial fibrillation in the setting of structural heart disease, the data are very, very limited for that. Studies are moving very slowly with FDA guidance, with very high complication rates that have been noted for that. So I really don't think in my own mind that there's a well-established role of catheter ablation as a curative procedure in atrial fibrillation in a vast

majority of patients and the small subset where we do consider that we may be moving in that direction would focal a-fib is a very different population than the population that we're looking for the deployment of this type of device.

DR. HARTZ: And then my final comments have to do with what I think is really the most serious issue. We have written all over these patient adverse events several terms. Incessant atrial fibrillation, persistent atrial fibrillation, chronic atrial fibrillation. When we looked at this protocol, we talked about chronic atrial fibrillation being a contraindication to this device.

There are a couple of mitral valve patients in these complications. Are there mitral valve patients who require -- are there patients, rheumatic patients who require a valve, who do not require Coumadin indefinitely who aren't in chronic atrial fibrillation? Yet, one of your patients you define as persistent atrial fibrillation greater than eight years. So could you define, the two of you for the Panel, what are these different definitions.

DR. SCHWARTZMAN: I think you can get into these nomenclature games. I think most simply put chronic atrial fibrillation is atrial fibrillation that cannot be converted. In other words, you can try -- you can deliver effective trans-atrial current and you cannot convert this rhythm.

Persistent atrial fibrillation is fibrillation which will not resolve itself, but which is amenable to resolution by shock or drug. The patient with persistent atrial fibrillation is meant to mean recurrent bouts of atrial fibrillation that do not resolve themselves. So the patient develops the atrial fibrillation, sits in it for X amount of time, presents with symptoms and there's intervention which resolves the atrial fibrillation until the next time.

The nomenclature, I agree, the nomenclature there which some people use incessant, some people use chronic. It's not appropriate in my mind, you're talking about paroxysmal which resolves itself. Persistent which resolves with aid and chronic which cannot be resolved.

A couple of problems there. One is

paroxysmal. How long do you wait until the atrial fibrillation resolves itself? Is that less than 24 hours? Is that less than an hour? Is it more than a week? These syndromes are all over the board.

Chronic. Who is the one telling you that you couldn't convert? So if I told you I had someone with chronic A-F that I can't convert trans-thoracically, I guarantee you that there's a number of patients in that group that I could convert trans-venously that are not converting just because you can't get adequate trans-cardiac current from a trans-thoracic shock.

So by nature you get smudging, but I think the most relevant definition relates to self-termination versus not and then not possible to terminate.

DR. GOLD: And I think, clearly, the duration of atrial fibrillation and the size of the left atria have been identified as predictors of those patients in whom atrial fibrillation cannot be converted back to sinus rhythm for any prolonged length of time. But certainly my own thinking on

quote chronic atrial fibrillation has changed dramatically with the ability of internal cardioversion and more importantly with some of the newer therapies and devices we have.

I now have 15 patients which I'll be reporting at the American College of Cardiology meetings who required ventricular defibrillators, not in this study, but a mean duration of atrial fibrillation of three years, one of which, a patient had 9 years of documented atrial fibrillation in whom we were able to cardiovert, give them a dual chamber fibrillator and they're all in sinus rhythm. So the horse is not always out of the barn simply because they have mitral valve disease of left atrium greater than 5 or whatever. The rules are not hard and fast. But if we're able to cardiovert them and get them into sinus rhythm for any meaningful period of time, we define that as persistent and not chronic atrial fibrillation.

DR. HARTZ: Yes, still three of these four patients who had strokes had quote incessant atrial fibrillation and serious structural heart disease.

All were at some point off their Coumadin. And actually, just for a hematoma, a patient is taken off Coumadin for two weeks and sent home with nothing. So these are practice of medicine issues. These are not device issues. Lovenox is never mentioned. Keeping the patient in the hospital longer are not mentioned. I think these are really serious concerns of mine that we just can't just assume it's a low risk procedure, put the device in and send the patient home, especially the patients that are this sick.

Two tiny things. Your patient number 4, one of the patients in your four, Dr. Schwartzman had an ejection fraction of 21 percent or 18 percent? Are these patients in the study because that's outside of the bounds of the standard deviation of the ejection fractions that were mentioned.

DR. SCHWARTZMAN: The patients were in the study.

DR. HARTZ: Because the lowest ejection fraction, if you read this protocol, was 33 percent. So this is a pretty sick patient.

DR. STANTON: No, the lowest was what?

Fifteen. The standard deviation both ways would just bring you 66 percent of the population.

DR. HARTZ: Okay, it was not the entire group. And then finally, what was the allergic reaction? What component -- one patient had an allergic reaction requiring an explant. What was that?

MR. HOLBROOK: My name is Reece Holbrook. I'm a clinical study manager at Medtronic.

If you give me just a moment, I'll find that patient in here.

DR. HARTZ: I don't ever remember seeing an allergic reaction to any lead --

DR. GOLD: I've had a couple of allergic reactions to titanium shells of devices. I've seen two over the years. They're pretty rare, but they're well reported. Occasionally, you need to coat the devices or otherwise the titanium that encases devices is known to cause an allergic reaction. I don't know what this one was.

MR. HOLBROOK: Okay. I found that patient. In the description it says dermatological

testing revealed that the patient was allergic to seven components of the device: polyurethane, silicone rubber, silicon medical adhesive, platinum iridium, perilune coated titanium, polysulfone, amber and epoxy.

DR. GOLD: That patient was not meant to have a device.

(Laughter.)

DR. HARTZ: That's all I have.

DR. GOLD: But again, I would reiterate your concerns and I share them fully about patient management, that Warfarin is required in patients with atrial fibrillation.

DR. HARTZ: We're sending all our valve patients home on Lovenox for an atrial fibrillation and we're bringing them in the hospital off Coumadin. We haven't seen this kind of stroke rate and these are patients are having surgery, so with more attention to the anti-coagulation protocol, I think you can avoid all of these issues, all of these problems.

DR. TRACY: Dr. Laskey?

DR. LASKEY: I don't want to belabor the

point either, but the stroke rate is just part of a larger concern I have with the numerical reporting of serious adverse events. But suffice to say at the end of my story, I think that's certainly -- the anticoagulation regimen should be part of the labeling.

I do have some concerns in the absence of a concurrent control group, how to interpret five strokes in four patients. That event rate is 2.8 percent, but if you put confidence intervals around that, you're getting up closer to 8 percent which is pretty high. So we've tried to establish the fact that there's nothing inherent in this device that's prothrombotic, nevertheless, this is a high stroke rate, a patient population of 144 who are at some undefined, but obviously dynamic risk of stroke. So I think as Mike and everyone else has said, the Coumadin thing should be de rigueur.

In our business, in interventional cardiology, we're held more accountable for complications and I'm going to look at the strokes and deaths as opposed to lead displacements for serious

complications. So there's four patients who had a stroke and as I read this, there were eight deaths in this series.

I assume that they're not overlapped. Apparently, none of the patients, these were nonfailed strokes. So that's 12 serious events in 146. That's a macerated 8 percent. That in our line of work is pretty high.

Any comments?

DR. STANTON: We'll walk through what the deaths were in just one second, so we can discuss it.

MR. BROWN: Just briefly related to classifications, of the eight deaths taking place during the study, first of all, none were classified as being related to the performance of the device. Seven of them were classified as nonsudden cardiac deaths and the eighth -- the classification of death was unknown. There's no information available on that, due to State statutory guidelines.

These patients, as I said before, were not device-related deaths per se, and in particular, the controlled time rates of death, the 6 and 12 month

Kaplan-Meier estimates of mortality are about half of what we saw in the 7019 decontrol.

DR. HARTZ: Why did they die? These are very health patients?

DR. STANTON: They're not very healthy patients because they had an ejection fraction -- how many had less than 40 percent ejection fraction? 31 percent had an EF less than 40.

DR. HARTZ: That's not very low. Really. Could you comment?

DR. GOLD: I think that the patients with heart failure and about 30 percent of these patients had a history of heart failure; 31 percent had ejection fractions less than 40 percent; a number of patients, I forget the exact number now, with coronary artery disease. So there's a lot of comorbidity in this group of patients which obviously some of these patients are going to die. That rate of death appeared to be consistent with what one would expect for a group of patients with that sort of co-morbidities and when compared with previous defibrillator trial in a somewhat sicker population

when corrected for that, there was no evidence of certainly any excess mortality associated with the use of the therapy.

DR. HARTZ: I have to be devil's advocate here. The mean ejection fraction was 51 percent. Patients with heart failure usually, if it's serious enough, die of VT. This is not a VT trial. This is an AF trial. I want to know why these patients died, all 8 of them and certainly the one that's unclassified has to be -- that's a sudden cardiac death. It would be in any type of literature.

So what did the patients with heart failure die of?

DR. GOLD: I have the proximate causes of death if you'd like to hear them.

DR. HARTZ: Okay.

DR. GOLD: There's one unknown. Other than that, the seven remainder are congestive heart failure, pneumonia, cardiogenic shock/respiratory failure, complications post-heart transplant, refractory heart failure and respiratory failure, hyperkalemia and ventricular fibrillation arrest.

DR. HARTZ: So you can take out the hyperkalemia and the post-transplant, but all the other ones still might have to be attributed -- you can't just say these are not device-related, trial related.

DR. DOMANSKI: You know, I really have a problem buying into that. We're doing a lot of -- we've done a lot of work in our shop with patients who are trying to prevent sudden death and/or patients who are at risk for sudden death, but who also have poor ventricular function.

Indeed, one of the difficulties with trying to reduce mortality in these patients is a lot of them do die of progressive heart failure. I mean -- and so I can't buy into that. I think that they've got -- they don't have a device that's going to prevent progressive heart failure and that's a well-known problem that we're facing. It's why we're doing some of the trials we're doing.

I probably shouldn't editorialize to this degree here, but one of the big questions it seems to me in this whole field of preventing sudden cardiac

death which is not the ones that Medtronic is addressing today is to try to pick out of high risk populations those patients who are not likely to die suddenly and from low risk populations those that are. If we could do that, we'd know who to put devices into, but they don't prevent progressive heart failure and that's a major cause of death in these patients. In fact, the sicker the patient, the more likely it is that they'll die of progressive heart failure.

DR. TRACY: I think another point that might help put this into perspective is if you could tell us were any of the -- the person who died of VF, was their VF backup turned off? Was there a predictor that that person could have had VF and were the deaths -- one was lung cancer. We'll just throw that out. Were the other deaths of the people with heart failure, were any of those unanticipated, for example, were they in the people with good ejection fractions or did they occur in people with bad ejection fractions?

DR. LASKEY: Or for that matter, since everyone is taking my precious time here --

(Laughter.)

DR. TRACY: I'll give you more.

DR. LASKEY: I suspect on my left there's more coming --

DR. STANTON: Can I just quickly answer the -- this is a question particularly about the VF death. That was one of the patients that did not get a device. So that's intention to treat, but did not have a device in.

DR. LASKEY: Just on this theme and thank you for that clarification, but I'm still concerned in the absence of concurrent controls how to interpret this and what do we do with the 7 point -- well, there's an incidence of VT/VF in this series of patient population that I being naive, of course, wouldn't have expected people to have. This was an AF population and you have some folks that snuck in because they weren't supposed to have sustained ventricular arrhythmias, but the few that got in there and yet you have a pretty hefty incidence here of VT/VF.

Now just for my own clarification what is

the rate of VT/VF or sudden cardiac death in AF literature, all comers? Is this higher or lower or the same?

DR. GOLD: Warren, I can't give you that number reliably. What I can tell you is that we did an analysis of the patients who had appropriate VF/VF in this group and not surprisingly there were a couple of predictors of that. The most potent predictor was having the presence of coronary artery disease in the left ventricular ejection fraction.

The group who had appropriate VT/VF had a mean ejection fraction of 29 percent versus 56 percent for patients who did not have VT/VF. So not surprisingly, at least to me and I think to most people, people with bad hearts have bad things happen to them. They develop heart failure. They develop VT/VF. They die.

And there was a group of patients with bad hearts and left ventricular systolic dysfunction who had the vast majority of the VT/VF episodes in this series, so I was reassured and not surprised and happy that we had backup therapy for these patients with

heart failure and left ventricular dysfunction.

DR. LASKEY: I think that's an important selling point here, but the general patient population of AF, the two individuals, the two teachers don't represent that end of the spectrum. And I think in terms of the risk benefit ratio I certainly wouldn't argue with this device being applicable for that group, but there are some concerns about it being applicable in the quote healthier group.

With respect to the interpretation of the complication rates, again in the absence of a control group, how is the 3X derived? Where does that come from? What does that do to the power? If you increase your confidence interval delimits, you decrease the power of a study and if you're decreasing the power of the study, what are we to take away from this, even though this is not strictly a comparative study?

MR. BROWN: The upper limit of 3 for the risk ratio was done, as you surmised, through a sample size power analysis. It was specified that we would have 80 percent power to detect the difference of 3

with a 70 patient sample size and that was done by assuming that the actual rate of complication in the 7250 would be equal to that of the 19D. So 70 patient sample size was the specified number for that power analysis.

DR. LASKEY: Thank you. Throughout -- one of the confusing things for me was to go back and forth between success rates by episode and success rates by patients and a lot of the data is presented as both and then there are these general estimate reportings.

When the intra-individual variation exceeds the inter-individual variation and that appears to be the case looking at some of these numbers, some patients just are loaded with arrhythmias and some have very few and so the exposure, if you will, is lower in some than in others. Does the GEE, in effect, is this adjusting for clustering? Is that what this --

DR. STANTON: Yes, it adjusts for multiple episodes in some patients and fewer than others.

DR. LASKEY: But that's different than

clustering, is it not? Just the fact that more patients have more episodes and maybe you're more likely to successfully treat more episodes, but there are differences in true exposure here. So the risk exposure is different.

Can you just clarify that?

DR. STANTON: I'm going to turn it over to the statistician.

DR. LASKEY: Okay.

MR. BROWN: Do I understand correctly that the question is the GEE estimate capable of accounting for time trends in terms of the fact that AF is a cluster phenomenon?

DR. LASKEY: That would be part of it. That would be part A.

MR. BROWN: Okay, then the answer to part A is no. What the GEE estimate does is effectively, it is calculating the probability of terminating in this example a random episode chosen from a random patient. What that means is for each patient you calculate the termination efficacy and then you average up those means. So it's an average of

averages is effectively what it does.

And that way it's capable of controlling so as to give each patient equal weight irrespective of the fact that some of them may have had many more episodes than others.

DR. LASKEY: Okay, so it's a quick and dirty regress to the mean.

MR. BROWN: Well, I don't know if I would cal lit quick and dirty. The actual methodology is very sophisticated and beyond my comprehension.

(Laughter.)

DR. LASKEY: Okay, I think I had one other, one other methodologic issue here.

Just one other point, are you recommending or would you recommend or should you recommend transesophageal echo, going through that exercise for these folks? I mean you've done that. You failed to find thrombus in this group and oh, by the way, these are patients who didn't have a stroke within the prior year, but again, these are folks who had clear-cut CVAs. So what would be your recommendations for the pre- and post-management of these folks in terms of

adjunctive either workup or pharmacology?

DR. STANTON: David, do you want to talk to that?

DR. SCHWARTZMAN: We do. We insist on a period of anticoagulation that is according to guidelines prior to implant and we do trans esophageal echo cardiography on everyone the evening of or morning of the implant.

Post-operatively, we give Coumadin on the night of the implant at a high dose and then the following day, depending on the INR we either initiate heparatin after 24 hours or send the patient home if they have a reasonable INR -- some of that is artistry, but that's what we do.

DR. LASKEY: I'm unclear. Is that in the labeling? Will that be in the -- that is your management strategy, but should we push for that?

DR. GOLD: Our management strategy, at least with your patients, Warren, is that we -- I don't mean to be redundant, but it's warfarin, warfarin, warfarin. We keep these folks anti-coagulated. We do a trans esophageal echoes only when

we think they've had inadequate periods of anticoagulation or if they're been in atrial fibrillation we're planning to cardiovert them, but if they're in sinus rhythm, particularly at the time of implant, if they've been adequate anticoagulated we do not routinely perform a trans esophageal echo on every patient who is going to undergo an implant, but I think it's mandatory to maintain the therapy that we know that works which is to maintain anticoagulation in these patients.

DR. LASKEY: I guess that's my bottom line and I think we all agree about that.

I would just like to commend the group for the quality of life analyses and issues. I think that's very, very important. Clearly, sometimes the fluff is more important than the hard data, so it's very elegantly done.

DR. STANTON: Thank you.

DR. HARTZ: May I have 30 seconds of Dr. Domanski's time?

I just have to go back to this because study exclusion criteria, NYHA Class 4 heart failure

and the protocol as I recall reading is mostly Class 1 and 2 patients. Should patients when they cross over into 3 and 4 be removed from the AF only treatment arm?

I mean I agree with you. They need defibrillators. And probably won't be long to getting to defibrillators, but what type of defibrillator and this was a study designed for 1 and 2 patients. That's my last comment.

DR. GOLD: At present, there's no clinical indication as you know to implant the defibrillator in the patient simply because they have heart failure. The SCD HeFT study are going on. The results of those we don't know at this point. If SCD HeFT or one of these other studies are positive, it may change our approach and thinking to those patients. But at present, those patients don't meet indications. Most of us do not routinely implant ventricular defibrillators simply because of the presence of heart failure and I think the back up defibrillation in this study simply was yet another benefit that the patients received, particularly those with left ventricular

dysfunction because we did pick up a significant group of patients who had those arrhythmias and were appropriately treated.

DR. HARTZ: That's clinical practice, but they're really excluded from this trial.

DR. GOLD: Only Class IV patients are clinically excluded. Class III patients are not clinically excluded. Class IV patients are essentially excluded from virtually every device-based arrhythmia therapy with the exception of those that are being used for primary hemodynamic purposes. All defibrillator trials exclude Class IV patients as well.

DR. TRACY: Okay, Mike, you're still sitting upright and didn't faint with that last --

DR. DOMANSKI: Well, we'll stay away from ventricular stuff today.

I'd like to get a little bit of a handle on these patients.

Please again go over the thing that makes then drug refractory. Go over that inclusion criteria for me. It's a simple question.

DR. STANTON: The definition was having failed one or more drugs.

DR. DOMANSKI: See, I guess I wonder about that as being drug refractory. It's a definition, but that doesn't strike me as a very high standard of anti-arrhythmic therapy in terms of saying somebody is drug refractory, particularly, I don't know what drug you used, but it's not -- it seems to me that these patients are not drug refractory in the usual sense of that term and so in fact, if one uses that as an inclusion criteria, I think one potentially could include a tremendous percent of the atrial fibrillation population under that indication. I mean if that ended up being the gateway and somebody enthusiastic about putting these things in, would in fact, implant them in an awful lot of the atrial fibrillation population. So I guess -- I don't think this is really a drug refractory group. I can appreciate the difficulty of recruiting for the study because it's a big deal to have a device placed and stuff like that and to randomized -- actually, they don't randomize patients, but the -- I guess -- I

think that's an issue. I think the indication the FDA is going to come down with if they use that is a very broad one actually.

Did you want to comment on that?

DR. STANTON: Just some other quick comments. The average number of drugs failed was three. At the time of implant, 40 percent of people were taking amiodarone. I think 20 was taking sotalol. So I think the fact that 40 had gone to amiodarone usually -- I'm not going to say it, speak for everybody, but usually it's not a first line drug

DR. DOMANSKI: I'm not so sure about that, actually. I'm using this first line drug and I think a number of people are using low dose amiodarones. I actually don't think that's true. Maybe someone else would want like to comment on it, but I don't know that that's a particularly controversial statement.

DR. GOLD: No. I agree. We use it more and more as a first line drug, but it also lowers my threshold for making patients drug refractory. Those who break through amiodarone, I'm less likely to move on to multiple other drugs. So it used to be

amiodarone would be a second, third, fourth drug, but once you sort of fail amio, you sort of fail drugs. It's often our perception.

DR. DOMANSKI: But I guess I would leave this part of the question by saying to the FDA that I think you're letting a huge percent of the a-fib population through the gate if the statement is they're drug refractory with one or more.

I think the other thing is, you know, I don't know how easily, knowing the technical excellence and I expect they can do this, I wonder if you can project the slide that shows survival free of atrial fibrillation at one year.

DR. STANTON: Free of -- if it's like first time occurrence?

DR. DOMANSKI: Well, do it for first time occurrence because that's being used. Do you have that? Is that projectable again?

DR. STANTON: No. We don't have a first occurrence analysis. We have how many were in sinus at the different follow ups. We have maintenance of sinus without going on to chronic atrial fibrillation.

DR. DOMANSKI: And are those people who may have had an recurrence in the interim?

DR. STANTON: Yes.

DR. DOMANSKI: Okay. Well, it's still an important point. If it were -- had it been timed at first occurrence, I would have expected this population to have a much higher rate of first recurrence than the people who -- with a defibrillator, the chances are if it's an effective device they are going to be in sinus rhythm at the time they're seen. So I guess that's perhaps a little less compelling than it otherwise would have been. But otherwise, you begin to wonder because one of the potential indications for this device is not so much somebody who is drug refractory, but I think one of the areas that needs to be investigated is whether or not if you immediately convert atrial fibrillation to sinus rhythm in people who are early in their atrial fibrillation history, whether you prevent remodeling that keeps people out of atrial fibrillation long term and that's why I sort of fixed on that particular data point, but I guess it's really not there.

I think with regard to the complications, this trial isn't powered, really. When you say that in terms of safety you're looking for something under a relative risk of 3, I mean if you have a relative risk of 3, I mean 3 times what the other type of therapy, geez, that's a huge risk.

DR. STANTON: As the upper 95 percent bound.

DR. DOMANSKI: Well, I know, but that's what you said you wanted to come below and you have a relative risk of 1.31.

On the other hand, a number of these deaths, for instance, the deaths don't appear to be device-related and when you have -- see, the way to design this trial if you were really trying to study this question would have been to randomize patients to standard therapy versus this device. In fact, this is one of the relatively few times when I think it might have really benefitted the application to have done that because the deaths that we're seeing are really not, don't appear to be device-related. The cerebral vascular accidents don't -- are not obviously

device-related. Now it sounds like they're more related to inadequate anticoagulation. In this day and age, one would expect these patients to be anticoagulated as folks have said.

So I guess I'm not impressed with those vascular accidents. Now a purist would say to me that perhaps if they hadn't been defibrillated they would have had the stroke despite the inadequate anticoagulation. There's no way of answering that, but I suspect if you'd done a controlled trial, where you really randomize these patients you might not have seen a difference in stroke rate. So I'm a little bit less impressed with that.

Also, lead dislodgements don't strike me as -- it's not good to have, but it doesn't strike me as a massive complication. So I guess we're faced, I'm left faced with a device I think probably is very effective in terms of terminating an atrial tachyrhythmia in a setting where clinical, the clinical benefit of that is unclear and this study I don't think can effectively answer it. But where it's really quite effective in doing that and where it's

not all that clear to me that there's a lot of safety detriment. As far as the -- the design of the study actually, I think, was unfortunate. I think they would have done much better with a more rigorous study. I think it actually would have proved their device was safe and effective.

I would also say that patient testimonials, particularly paid testimonials are not the way I would try to demonstrate safety and efficacy of one of these things.

I really don't have any other comments.

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: We haven't heard Jim Dillard's golden tones all morning. So I want to start with a process question.

(Laughter.)

And that is really what is -- in a device this complex, are we in an all or nothing setting? Is this simply a yes or no to the can and everything that's in it or are we in a position to identify certain elements or performance features that might be more safe and effective versus others that would be

less safe and effective with a mandate to clamp some and release others?

MR. DILLARD: Yes.

(Laughter.)

MR. DILLARD: You do have the opportunity to make any recommendation to us that you would like and if your recommendation would include some subset or something like that that you would agree on. I would also like you to discuss the whole item also and to give us a recommendation, but that's okay.

DR. KRUCOFF: Software, hardware, is not an issue, it's just a question of being specific.

MR. DILLARD: Jim Dillard, I mean it cna be an issue if by an issue you mean can you have a discussion of it and could a recommendation include something that was less than the complete package that you currently see, it could include that, yes.

DR. KRUCOFF: And one other quick -- I'm a plumber, so I have to ask you electrical guys more educational questions. My understanding is that the current version of the device in its hardware configuration is implanted essentially identically to

the way the previous approved device is implanted. Is that including a ventricular lead?

DR. GOLD: Yes.

DR. KRUCOFF: And including a ventricular lead that can defibrillate or pace the full range?

DR. GOLD: Yes.

DR. KRUCOFF: And I know in our ICD patients that means that when we test that lead we fibrillate the patient, the ventricle. Is that also what you do with these a-fib only patients? Do you test the ventricular defibrillation capability by fibrillating the ventricle?

DR. GOLD: Yes. It's required that they have an adequate ventricular defibrillation threshold to implant the device.

DR. KRUCOFF: Okay, so you do the whole thing. Okay.

Well, I'm -- I think I can honestly say of every set of data that I have reviewed in the past five years, I've spent more time with this set of data than any and I find it, the word that comes to mind is impenetrable in terms of determining the truth. It

seems to me that we have a very complex device that has some really exciting potential, design features. Obviously, you guys have put an enormous amount of thought, finding these patients, enrolling them, tracking them, the quality of life segment. I mean there's an enormous amount of work involved in this and the potential of the device for patient population who do live with an enormous amount of misery. I mean even as a plumber, the number of patients we re-cath because they have recurrent a-fib and progressive a-fib and then they feel a little funny in their chest, so people are worried about is their ischemic disease progressing. It's a mess. These are a true misery-laden array of complex patient management.

So I am 100 percent with the agenda of trying to advance our ability to help these folks. It's just that when I go through these data, it's a Rorschach and I think you can make whatever you want out of it. I think you guys have done an elegant job this morning of showing these sort of rays of light that suggest the potential right down to the patient testimonies of how much impact this can have when it

works on a human being who suffers from intractable atrial fibrillation. My problem is that particularly as Mike said on the safety side, you can make a Rorschach that is the opposite side of the picture and that is to look at, a lot of these complications, including the deaths, as the potential result of subclinical emboli. I mean stroke is not the only result of tossing clots out of the heart. And whether you toss them from the right side or the left side or whether they end up in the lungs or whether they end up in the coronaries, whether they ultimately cause these occult and particularly if you are defibrillating and defibrillating and restoring sinus rhythm and restoring sinus rhythm and at least our teaching still includes the potential that particularly off Coumadin, when you restore sinus rhythm may be when the mechanics of the atrium that make you symptomatically feel better begin, that's also the mechanics that can dislodge or throw out whatever debris has managed to accumulate during the fibrillating static period is an ugly and scary way to look at these same data. And I don't know what the

answer is. That's my dilemma here. I cannot discern from these data how in the world we would know what the truth is. s And I can imagine that trying to conceive a randomized clinical trial in this patient population would be a huge and difficult challenge. You had a long time to find these patients from a lot of sites, but I really wonder whether a randomized clinical trial wouldn't have gotten you a whole lot further in understanding how the device works, what role it is playing, whether these deaths, I mean you guys have sat here and said three times that there were no deaths in this study. There are not no deaths in this study. And whether the deaths are device-related or not, that's a different question. But there are deaths that might be related to the device from sub-occult clinical events that outside of a randomized trial with appropriate controls and that's the dilemma here, is the control population for an IC population, it's really apples and oranges. I don't know how to compare the outcomes.

You do risk adjustment -- to me, traditionally, we do a risk adjustment when we have a

patient population whose outcomes are worse and we think they're worse because the patient population was sicker than the controls, so we risk adjust to see if, in fact, the worse outcome is not because the device or the therapy is doing anything. It's because the patient population substrate was more ill.

Here, it's very clear that these patients are less ill by inclusion and exclusion criteria and by the descriptors of the actual enrolled patients, but we're risk adjusting to understand whether the reason that they appear to look worse -- I don't know if this is the IFU -- the first section of the pack you call prescriber's package insert. In Table 11, and this is only a 6-month actuarial curve, these 95 percent confidence intervals do not overlap.

Now this is the whole 303 patient denominator of the 7250? But if we're going to assume that the ICD application here has not deteriorated in outcomes relative to your previously approved data --

DR. STANTON: Those confidence intervals overlap. We could give you the raw data.

DR. KRUCOFF: Okay, well, I'm just looking

at the graph that's here and these confidence intervals.

DR. STANTON: I think they do. The upper bound of the -- the upper bound is above the lower bound.

DR. KRUCOFF: Maybe that's an optical illusion.

DR. STANTON: We can give you the raw data also with the confidence.

DR. KRUCOFF: I'll buy that because I was going to ask that. The numbers do overlap, but the trends consistently for this a-fib population are worse, not better. Granted, that's not significant and that just gets back to my first point. I don't know how to tell what the truth is here. But I think the potential that all of the electricity that's being thrown at the heart, all of the low voltage electricity which has effect even though two thirds of the time it's not a therapeutic effect, we're throwing a lot of complexly protocoled electrical stimuli at people's hearts with at least one interpretation of these data being that that may do things that we don't

anticipate that are of the adverse kind and with a controlled population here being an ICD population, I don't know how to understand this definitively as true that we're -- obviously we benefit some people, but we've learned that lesson before in medicine. You can benefit one and harm three and if the harm is occult, it's not until you do a randomized clinical trial that you will ever be able to determine that. And apart from just the procedural issues where to me it may not be a complication if you have to replace a lead, but if you have to keep the patient off Coumadin for an extra couple of days in order to replace a lead and they have a stroke which is the scenario of at least one of these patients having a hematoma in the pocket, I mean we are talking about a procedure whose secondary and tertiary elements may ultimately relate to harm. And for a patient population who largely are sick with misery, the potential to do harm, I think has to be respected and I am just left with a forest of data of incredibly complex nature and a wish that at some level either you had just decided up front to do this in a randomized fashion where the control

population were interpretable and not by obtuse statistical modeling, but by actually being from the same clinical patient population so that we could understand whether the low voltage electricity that in 1 in 3 seems to be a freebie, I think was the term you used, well, it's not clear to me that the other 2 out of 3 are not freebie. And similarly with the shocks, there's a lack of ability to document in the patient activator how many times the patients, at least from what I read, you're not acquiring information or able to archive information on the specificity of the use, just the sensitivity.

So there are so many pieces and I don't want to go on and on, but to me the real issue here is in a complex data set on a complex instrument, what the truth of who we help and who potentially hurt is a dilemma and I feel for the dilemma because this patient population is a dilemma. But it's obvious from the interpretation and from the very first slide and to the two patients who were kind enough to join us and give testimony, that your vision of this is the benefit and you're obviously here to discuss the

benefit and I understand that. I just am left with a data set that makes me scratch my head. In fact, worse than that. It makes my head ache after review in detail. I think there's another message that could easily hide in this data set and I don't know how to determine one or the other, other than to do a proper randomized control trial with a control group who are appropriate for this indication.

DR. TRACY: Mike?

DR. DOMANSKI: Let me ask a question. I guess -- obviously, a control trial makes it very easy to sort it out. We don't have a control trial. So the question is we need to kind of -- with tweezers, kind of pick out what we know here so we can make some recommendation to the FDA that's appropriate from a regulatory point.

How big a trial would have been necessary? If we're going to talk about a randomized trial, we also have to talk about something that's practical. It has to be doable.

Have you done the sample? Maybe your stats folks have done a sample size. If you used as

an endpoint of a randomized trial death or CVA or just CVA alone, have you runt hose numbers at all? Do you have a sense of the sample size?

MR. BROWN: Looking at those specifically as endpoints, we have not run an analysis. In fact, we haven't done any analyses of what the likely size of a randomized trial would be.

Looking at those specific endpoints --

DR. DOMANSKI: You certainly have event rates. You wouldn't have any trouble with your assumptions there.

MR. BROWN: Exactly. Certainly the data is available. We haven't actually done that analysis. My guess, just off the top of my head, statistically, is that that would be a very large sample size due to the relatively low event rates.

DR. HARTZ: They're not low in this series.

DR. LASKEY: That's the point, they're not low in this series, but they're low in the general literature. It would be huge by --

MR. BROWN: I apologize. When I say low,

I'm just referring to absolute numbers, 10, 12, 8 --

DR. DOMANSKI: There's another point too about that. I don't think these deaths sound like they're device-related. So the problem is that the separation would have to come in the CVA. I mean if both groups are having the same number of nondevice-related deaths, I mean that doesn't help you. So death or CVA may not, in fact, be a very good endpoint. It may be CVA and it may be what one is asking for is a massive trial, so it may not even be --

DR. KRUCOFF: I would go a much simpler route and I think that death and CVA is a safety issue, but your power of trial efficacy and I think you have some wonderful endpoints. In fact, you have some very suggestive observations, I think, about behavior over time, about the accumulated or added or accrual of benefit over a one year follow-up for arrhythmia burden, for quality of life. You could power efficacy, I think to a relatively nominal level and then in a properly randomized controlled group. you'd be able to look at some of the safety issues

about death and stroke and feel comfortable that while you don't power a trial off that, at least you could be comfortable.

DR. TRACY: I think I'm going to jump in here and say we're not here to redesign a trial. We're here to decide on the information that was presented to us whether we have data that can support our --

DR. DOMANSKI: At the same time if they turn us down we're going to be asked to do it and the question are we going to be asked for something -- let me just pursue this for a second. I don't agree with that. I think if you a power a trial on your efficacy endpoint you're not going to have the power to do your safety analysis and that's what we're all worried about. The device is effective in converting the rhythm. I think they've demonstrated efficacy for that. They haven't demonstrated clinical -- that helps you clinically. But in fairness, they've demonstrated that you can get somebody in, I think, is my opinion, they've demonstrated that they can effectively put somebody from atrial fibrillation into

a sinus rhythm which I think is a meaningful endpoint and I would, despite my lack of enthusiasm for the overall design of the study, I think they've demonstrated efficacy.

The concern that remains is safety. My concern doesn't relate to death, as a matter of fact, and I don't think there's a subtle mechanism going on. It's exactly what we're seeing in the other studies that we're doing and they have nothing to do with this.

I guess the stroke thing is a little, is a little tougher, but I wonder if one couldn't tease out of what they've got, the people who actually had the strokes. That is, if everybody who was adequately anti-coagulated in their study did fine and they had four strokes and they were all from a group of people who were, in my view, inappropriately because in this day and age when you have people in and out of a-fib who are of a certain age, I use 60, other people use 65 or who have structural disease, those people are anti-coagulated, continuously.

DR. GOLD: Of the four patients who had

strokes in the series, three were not on anti-coagulation, so in terms of the first question about power, even if you take all the patients, 4 out of 146, I'm not a statistician, but that's going to be a load of patients if you're going to try to show that that is significantly higher than some other population, given the number of studies who already have with warfarin showing stroke rates in that population.

DR. TRACY: The only issue would be -- now the three 3 of the 4 that had strokes were off of anti-coagulation and I think you can't -- the only thing that raises is were they off of anti-coagulation because of some device-related complication? Otherwise, they were just being under anti-coagulated and so can you answer that question?

DR. STANTON: Yes, one had had a hematoma and it had been stopped, but how long before?

DR. GOLD: One had a hematoma two weeks out from the procedure and had a stroke six weeks out from the procedure, so again, my clinical practice, if a patient has a hematoma, I'm going to evacuate the

hematoma. A month later, that patient is going to be on anti-coagulation, an atrial fibrillation patient. I actually initiate anti-coagulation immediately on that group of patients. So was it related? Yes. But it was a practice of medicine issue in my mind that a month later the patient still has not been anti-coagulated and had a stroke.

DR. TRACY: Would you might just going through those -- the other three people just so we can -- if we have that information?

I'd like to hear this before we go on.

DR. HARTZ: No, it's the same patient. I read it differently. I read it as though the patient got the hematoma immediately. The Coumadin was stopped for two weeks and the patient was put on aspirin. Who would -- that's the way I read it. The patient had a surgical hematoma.

DR. TRACY: Either away it's an inappropriate -- the patient was not anticoagulated because of a device complication and if we could just get those other three.

DR. KRUCOFF: There's another issue here

that was mentioned earlier as to whether this device can or should be approved independent from data that show that systematic anticoagulation recommendations concomitant with current practice of medicine would, in fact, make some of these things disappear and belongs in the labeling of the device. DR. GOLD: I agree.

MR. HOLBROOK: Okay, the first patient had no anticoagulant therapy at the time of the event.

DR. TRACY: At the time -- I'm sorry?

MR. HOLBROOK: At the time of the event, the patient had delivered patient activated therapy on days 2, 3 and 4 prior to the event.

DR. TRACY: And there was no device-related reason why anticoagulation was stopped?

This was the hematoma man or woman, whatever, any others?

MR. HOLBROOK: The only other patient who had ceased their anticoagulants for device-related reason was at implant and that was a patient who had a stroke one day after implant or after pre-hospital discharge.

DR. LASKEY: And the one who had two strokes, what was that story?

MR. HOLBROOK: The one with two strokes was the patient who had -- was on Coumadin and had a shock within 4 days of the first stroke and then 12 days after had a second stroke.

DR. LASKEY: You see, I'm sure we're not here to discuss the natural history of stroke, NAF. But these patients in order to get in this study had to not have had a stroke within the year prior to the participation in the trial and then all of a sudden there is this quote cluster or a bunch of events occurring in the setting of the trial.

Any way you cut it, the stroke thing and AF is a clustered event and the highest risk is around the time of the first event and then it trails off like all other time-dependent phenomenon.

What is going on here that they're stroke-free for a year or maybe two or maybe three and then they participate in the trial and then there is a blip which is a fairly significant blip, if you compared this to any of the literature in the AF

population, except for the highest risk category?

DR. TRACY: What you've said so far is we have two strokes that were related to something related to the procedure, either acutely when the procedure was done and when Coumadin was stopped. The second because of hematoma. So there's those two. So those are of concern because of that and then this third person. I think the thing that Dr. Laskey is getting at, you have a person who has a stroke and then has a shock and then has another stroke. Is there some indication or warning that we should put in here somewhere that if a person has a CBA while on this therapy, that the device should be deactivated for a period of time.

DR. STANTON: Yes. Well, I think it gets back to a point that Michael has really pointed out about the importance of anticoagulant therapy.

DR. TRACY: But this was an anticoagulant -- the one with the two strokes was anticoagulated.

DR. STANTON: Right. And in patients on Coumadin, large studies have shown there's about a 1.5 percent per year rate of stroke.

DR. TRACY: But clinically, I'm not so sure that any of us would two days after a stroke would cardiovert somebody and I think that's --

DR. STANTON: Right --

DR. TRACY: That might be something that we have to consider.

DR. STANTON: That's a good point.

DR. GOLD: I think the randomized literature of warfarin and there are seven or eight high quality studies suggest that stroke rates in patients on warfarin are on the order of 1 to 2 percent per year or so and those patients who are not on warfarin are on the order of four to five percent per year. We can argue, quibble a little bit over those numbers, but there were four patients who had strokes out of 146 patients in this series which are going to give us a rate somewhere in the 3 percent or so range over mean follow-up about a year. So I think the stroke rate in this series falls within the well documented stroke rates for patients in randomized clinical studies of warfarin and if we look at the patients who had strokes, one patient had a stroke on

Coumadin well within the range of where other studies of Coumadin, in the absence of device had strokes and the number of patients who had strokes in the absence of Coumadin had higher rate of strokes and again, well within the range that had been reported previously for other series.

And while I can't exclude that none of these strokes were absolutely related to the device, the numbers that we did see are typical for the numbers that have been reported in the literature and certainly our experience with the firm and other studies when you have a-fib patients, they tend to have strokes. They're low rates, but these were low rates as well.

DR. KRUCOFF: What about this as another -- what is the truth here? What about the VT/VF folks? Have you represented as having been protected by having their device in for an atrial fibrillation indication who just happened to be VT/VF and were saved by their device.

Out of a patient population who were specifically screened to exclude VT/VF, 11 out of 140

some patients with 67 episodes, just again, I don't know what the truth is.

DR. STANTON: Well, the study excluded people with a history of sustained VT or VF.

DR. KRUCOFF: Right.

DR. STANTON: Thirty-one percent of the people had an EF less than 40 percent. This is a relatively high risk population for death by sudden death and so I don't think it's surprising that some of these patients had recurrent episodes of VT and VF and in fact, we're not trying to make the case this way, but it was to their benefit that there was ventricular backup therapy. Some of those patients likely would have died.

DR. KRUCOFF: Right, and this is where I'm saying a randomized trial would help because these also happen to be patients all of whom had their ventricles instrumented who had never historically -- I mean, you're right. The natural history of the patients with low EF or ischemic heart disease is a higher likelihood at some time of including ventricular dysrhythmia, but to make that convincing,

it would be nice to know that actually instrumenting their ventricle and creating a lot of additional electricity low and high voltage around the heart doesn't have some sort of other effect that makes almost 10 percent of this population evidence 67 --

DR. GOLD: I would suggest that if you look at the greatest benefit of defibrillators, we can argue about that, but in my mind the greatest of defibrillators is documented in the medical literature as primary prevention from the MUSTT and the Mader study show a greater benefit than any of the secondary prevention studies. Yet, that is a population by definition had no history of sustained VT or VF.

So simply having the substrate there, the patients who got instrument with a defibrillator in both series had about a 50 percent lower mortality with defibrillators compared to not having devices. So I think there's certainly a well-established precedent that defibrillator therapy can be useful in patients without already having survived an episode of sustained ventricular tachyarrhythmias.

DR. DOMANSKI: Well, I actually have a

problem with that interpretation of the MUSTT study. It's not true that they hadn't shown sustained VT. It's true they hadn't shown it outside the EP lab. But it appears that the group that's inducible is, in fact, a different group. That is, those are specifically the people who -- MUSTT was a trial where -- MUSTT was a trial where patients had to -- to get into the study, had to have inducible VT, inducible int he EP lab. So that's a group of people that clearly has a substrate to produce it. So it's a little different from this group. I mean there's no demonstration in this group that they have a substrate in the EP lab.

I think the other thing, the other thing, by the way about this stroke rate is that the a-fib population on Coumadin does have a CVA rate, so I mean go through this sort of mental gymnastic of planning this trial for some kind of event, so that you look at event rates, you'd expect there to be one or two CVAs in this population, even if they hadn't put a device in. So now you're looking for minuscule difference.

You can see if you'd done this study, even

though it would have been grossly underpowered, and you had a stroke or two in the other group, this discussion would never have taken place, interestingly, even though it would have been grossly underpowered, compared to the study that you're liable to get recommended to you by this group.

it's an interesting thing. I don't think you can do a controlled study for safety on stroke in this group so there's no point in disapproving this thing and then telling them to go do it, because I think the event rates are going to be too low.

DR. TRACY: Yes. I think the very fact that it took two years and I was wrong, initially, it's more than 113 centers. It was 140 centers or something, to come up with 146 patients in two years, you'd have a study that would last maybe 50 to 60 years.

DR. DOMANSKI: Well, I think the recruitment rate could be dramatic -- I'm not sure why they had quite so much trouble --

DR. STANTON: It was 50 centers.

DR. TRACY: You have listed there more

than that. You have listed something like that -- you have U.S. 107 sites, 33 European sites and 6 Canadian sites.

DR. GOLD: One hundred seven patients came from the United States; 33 from Europe, and 6 from Canada to make 146.

DR. TRACY: I see.

DR. DOMANSKI: Even if you did this study in all comers in a-fib, you'd never get the kind of numbers you wanted.

DR. STANTON: Maybe I can just make -- did you want to speak?

DR. TRACY: Just to the -- Mitch's question of is there some unforeseen thing that is happening to the ventricle. If you can tell us, if you noticed any worsening in ejection fraction in the patient population, I think that would be reassuring. I'm assuming not. I'm also pretty confident in the use of devices. I think that the days of significant pro-arrhythmia of ventricular pro-arrhythmia with devices is gone. I don't think we see that any more, but just to answer this question specifically, did

anybody's ventricle get worse?

DR. STANTON: While they're looking to see if we have those data, let me walk through again the eight deaths since there's a lot of discussion about that. One was -- remember one of the two people who was intention to treat did not receive a device. That was the VF death. Don't know the ejection fraction on that patient.

Of the other seven, we have the ejection fraction of 5 of them. It was 40 percent; 20 percent; 20 percent, 62 percent, that was a respiratory failure death; and 20 percent. The two people who we didn't have in EF documented on were said to have died of congestive heart failure and refractory heart failure and respiratory failure combined.

I want to also emphasize that all of the deaths were reviewed with all the information we had by an independent adverse event committee of independent outside physicians who were not involved in the clinical trial.

DR. SCHWARTZMAN: Can I comment on the ejection fraction? This is data that was submitted